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09/679,664	10/03/2000	Thomas M. Stormann	072827-1801	7662

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EXAMINER	
LANDSMAN, ROBERT S	

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1647	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/679,664	Applicant(s) STORMAN ET AL.	
	Examiner Robert Landsman	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *12-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☒ Claim(s) *1-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Preliminary Amendment A, filed 6/18/01, has been entered into the record.

B. The Information Disclosure Statement, filed 6/25/01, has been entered into the record.

C. The Sequence Listing, filed 6/18/01, has been entered into the record.

D. Claims 1-41 are pending in the present invention and were subject to restriction in Paper No. 11, filed 3/13/02. In Paper No. 12, Applicants elected Group I, claims 1-11, with traverse. However, since no traversal was provided with the response of Paper No. 12, this election has been treated as an election without traverse. Therefore, this restriction is deemed proper and is made FINAL.

PM

E. The syntax of claims 7-9 can be improved by adding the word "receptor" after the word "fusion."

2. Oath/Declaration

A. The Oath/Declaration is objected to since the printed name of Thomas Stormann does not match the signature. The printed name "Storman" only has one "n," whereas the signature and Filing Receipt have two "n"'s.

B. The Oath/Declaration is objected to since non-initialed and/or non-dated alterations have been made to the Residences and/or Post Office Addresses in the oath or declaration for the following inventors: Laura Storjohann, James Busby and Rachel Simin. See 37 CFR 1.52(c). A new Oath/Declaration is required.

3. Specification

A. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title recites "G-protein fusion receptors and chimeric GABAb receptors." However, the claims are also drawn to nucleic acids encoding these fusion proteins and methods of making these proteins. Furthermore, the way the claims read, the chimeric protein does not have to comprise any domain of a GABAb receptor.

B. The specification is objected to since there are holes punched through words at the top of pages 2-17, 19-25, 27, 28, 30-33 and 35-40. Applicants are required to submit new pages (MPEP 608.01; 37 CFR 1.52(b)).

C. Though the specification is not being objected to for this reason, in the first line of the specification, Applicants are not required to recite the first inventor's name for the provisional application from which the present application claims priority (Garrett et al.).

D. The Figures are objected to since Figures, "5J," "11L," "13L," "13M" and "16A"-"16E" are written in upper-case letters, whereas the rest of the Figures are in lower-case.

E. The specification is objected to since many characters (such as the Greek symbols, α, β and γ) appear to be missing from the disclosure. See, for example, page 2, lines 20-21; page 12, line 31; page 13, lines 2, 3, 13, 19-21 and 32; page 15, line 33; page 17, line 13).

5. Claim Objections

A. The syntax of claim 1 could be improved by placing a colon after the word "comprising" as well as separating the five components of the claims ("an extracellular domain," "a transmembrane domain," "an intracellular domain," "an optionally present linker" and "a G-protein") by reciting parts "(a)," "(b)," "(c)," "(d)" and "(e)," respectively, before each of these components. Claims 2-11 are also objected to since they depend from claim 1.

B. Claim 5 is objected to since the claim does not end with a period. Claims 6-11 are also objected to since they depend from claim 5.

C. Claims 7, 8 and 11 are objected to since the recitation of "any one of claims 1-6" is an improper Markush Group. Therefore, claims 7, 8 and 11 should be amended to recite, in the alternative, "any one of claims 1-5, or 6." Claims 9 and 10 are rejected since they depend from claim 8.

6. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a G-protein fusion protein comprising an extracellular domain, a transmembrane

domain, and an intracellular domain comprising one or more of an extracellular domain, a transmembrane domain, and an intracellular domain of one or more of a CaR, mGluR, or $GABA_B$ receptor, does not reasonably provide enablement for a G-protein fusion protein comprising said domains from said receptors which are "**substantially similar**" to said CaR, mGluR, or $GABA_B$ receptor domains, or in which the intracellular domains from said receptors comprise only "**at least about 10 amino acids**" from said receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive regarding all G-protein fusion receptors which comprise domains which are "substantially similar," or which comprise "at least about 10 amino acids" to known CaR, mGluR and $GABA_B$ receptor domains. "Substantially similar" is defined in the specification as a domain having "at least 40% sequence similarity between respective polypeptide regions making up a domain" (page 3, lines 13-20). Therefore, domains which are "substantially similar," or which comprise "at least about 10 amino acids" to the claimed domains would comprise proteins with one or more amino acid substitutions, deletions, insertions and/or additions to known CaR, mGluR and $GABA_B$ receptor domains.

Applicants provide no guidance or working examples of protein domains which are "substantially similar" or which comprise "at least about 10 amino acids" of a CaR, mGluR, or, $GABA_B$ receptor domain other than those domains of CaR, mGluR, or, $GABA_B$ receptors known in the art (see, for example, page 22, lines 25 – 33 and page 27, lines 25-27), nor do they recite in claims 1-8, 10 or 11 that the fusion receptor has to be functional, or, more importantly, what this function is. In claim 9, Applicants do recite that the G-protein fusion [receptor] is "functional." However, Applicants do not provide a *function* of this fusion receptor. The only function that Applicants disclose is the initial step of receptor activation is signal transduction through a G-protein upon the binding of a ligand to the extracellular domain of the fusion receptor (page 6, lines 11-14 and, e.g., "calcium-activated chloride current – Example 2 of the specification) and, therefore, Applicants are not enabled for any and all functions of a G-protein fusion receptor. Furthermore, it is not predictable to one of ordinary skill in the art how to make

a functional G-protein fusion receptor comprising domains other than those comprising the domains of known CaR, mGluR and $GABA_B$ receptors (i.e. domains which are "substantially similar" or which comprise "at least about 10 amino acids" of a CaR, mGluR, or, $GABA_B$ receptor).

In summary, the breadth of the claims is excessive regarding all G-protein fusion receptors which comprise domains which are "substantially similar," or which comprise "at least about 10 amino acids" to known CaR, mGluR and $GABA_B$ receptor domains. Applicants provide no guidance or working examples of protein domains which are "substantially similar" or which comprise "at least about 10 amino acids" of a CaR, mGluR, or, $GABA_B$ receptor domain, other than those known in the art, nor do Applicants provide a *function* of these fusion receptors. These factors, along with the lack of predictability to one of ordinary skill in the art as to how to make a functional G-protein fusion receptor comprising domains other than those comprising the domains of known CaR, mGluR and $GABA_B$ receptors, leads the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

7. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 5 is confusing since there appears to be a character missing between the characters "G" and "15" and "G" and "16." This character is likely an "α," but since Gβ and Gγ also exist, the claim is unclear. Claims 7-11 are also rejected since they depend from rejected claim 5.

B. Claim 6 is confusing because it is not understood how a $GABA_B$ receptor sequence can be from a mGluR since these are different receptor types. It appears as if the final recitation of "mGluR" should be "$GABA_B$." Claims 7-11 are also rejected since they depend from rejected claim 6.

C. Claim 10 recites the limitation "nucleic acid" into claim 9. There is insufficient antecedent basis for this limitation in the claim.

D. Claim 10 is confusing since it is not clear from the claims or the specification what "elements" are being used for introducing a heterologous nucleic acid into the claimed cell.

E. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: recovering the fusion protein from the culture.

8. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuller et al. (reference A6 on the Form PTO-1449, filed 6/25/01), in view of Bertin et al. (reference A27 on the Form PTO-1449, filed 6/25/01), further in view of Negulescu et al. (reference A20 on the Form PTO-1449, filed 6/25/01), further in view of Kaupmann et al. (reference A11 on the Form PTO-1449, filed 6/25/01) and further in view of Rock et al. (Vaccine 14:1560-1568, 1996). Claim 1 recites a G-protein fusion receptor comprising an extracellular domain, which comprises the extracellular domain of either a CaR, mGluR, or a $GABA_B$ receptor; a transmembrane domain which comprises the transmembrane domain of either a CaR, mGluR, or a $GABA_B$ receptor; and an intracellular domain which comprises the intracellular domain of either a CaR, mGluR, or a $GABA_B$ receptor; an optionally present linker, and a G-protein. Claim 2 recites that the G-protein fusion protein consists of the extracellular, transmembrane, and intracellular domains of claim 1. Claim 3 recites that the linker is 3-30 amino acids in length. Claim 4 recites that the linker is not present. Claim 5 recites that the G-protein is G[α]15, G[α]16, Gqo5, or Gqi5. Claim 6 recites that any CaR, mGluR, or $GABA_B$ receptor sequences are human. Claim 7 recites a nucleic acid comprising a nucleotide sequence encoding for the G-protein fusion [receptor] of any of claims 1-6. Claim 8 recites an expression vector comprising a nucleotide sequence encoding for the G-protein fusion [receptor] of any of claims 1-6 coupled to a promoter. Claims 9 and 10 recite recombinant cells comprising vectors expressing functional G-protein fusion [receptors]. Claim 11 recites a process for producing a G-protein fusion receptor.

Fuller et al. teach a G-protein fusion receptor comprising an extracellular domain, which comprises the extracellular domain of either a CaR, or mGluR; a transmembrane domain which comprises the transmembrane domain of either a CaR, or mGluR; and an intracellular domain comprising which comprises the intracellular domain of either a CaR, or mGluR (Figures 1A – 1F and column 16, lines 23-

26. The claims meet this portion of the limitation of claims 1 and 2 since it is not required that the G-protein fusion protein of claims 1 and 2 of the present invention comprise any portion of a $GABA_B$ receptor. Fuller et al. do not teach the presence of a linker in their fusion protein, the absence of this linker being a limitation in claim 4 of the present invention. However, Fuller et al. do also teach human CaR and human mGluR (Example I, column 46, lines 37-38 and lines 54-59), nucleic acid molecules comprising these fusion receptors (Examples II and III in columns 46-47), recombinant cells comprising these nucleic acids and expression vectors and a process for producing these G-protein fusion proteins (Examples 6 – 8, columns 49 and 50). These nucleic acid constructs are inherently coupled to a promoter since the fusion proteins are expressed. The G-protein fusion proteins have also been shown to be functional based on their ability to measure intracellular calcium release (Example 9, columns 50-51 and Figure 9), which is a signal transduction event through a G-protein.

Fuller et al. do not teach a G-protein fusion protein comprising a $GABA_B$ receptor, including human. However, Kaupmann et al. do teach human $GABA_B$ receptors (Abstract and SEQ ID NO:3, pages 56-62). Though this reference is not required to meet the limitations of any of the claims in the present invention, since a fusion receptor comprising a domain of a $GABA_B$ receptor is not required, it is being provided in anticipation of an amendment to the claims to require that the G-protein fusion receptor comprise at least one domain of a human $GABA_B$ receptor. It would have been obvious for one of ordinary skill in the art at the time of the invention to have produced a fusion receptor comprising at least an extracellular, transmembrane, or intracellular domain of a $GABA_B$ receptor fused to one or more of these domains from either a CaR or mGluR, or both, by substituting the G-protein coupled $GABA_B$ receptor of the present invention for the G-protein coupled CaR and/or mGluR of the present invention since all three of these receptors are G-protein coupled receptors. One of ordinary skill in the art would have been motivated to have produced these chimeric receptors since it was well-known at the time of the present invention that domains from these different G-protein coupled receptors can be substituted in order to identify various ligand-specific, G-protein-specific, and functional domains of these receptors (Fuller et al. column 7, line 66 – column 8, line 18). The artisan would have had a reasonable expectation of success in producing these fusion receptors since the DNA for all of these human receptors was known and the technology to produce fusion proteins was well-known and highly successful in the art at the time of the invention.

Neither Fuller et al. or Kaupmann et al. teach a fusion protein which comprises a G-protein. However, Bertin et al. do teach a G-protein fused to a G-protein coupled receptor (Abstract and Figure 1). Though Bertin et al. do not teach a G-protein coupled to a CaR, mGluR, or $GABA_B$ receptor, it would

have been obvious for one of ordinary skill in the art to have substituted one or more of the G-protein coupled CaR, mGluR, or $GABA_B$ receptor of the present invention for the G-protein coupled β2-adrenergic receptor of Bertin et al. since all of these receptors are coupled to G-proteins (Fuller et al. column 1, lines 64-66; column 9, lines 3-8). Therefore, the artisan would have had a reasonable expectation of success in substituting the cDNA encoding a CaR, mGluR of Fuller et al. and/or $GABA_B$ receptor of Kaupmann et al. into the polycloning region used for the β2-adrenergic cDNA of Bertin et al. (see "Construction of the Expression Vector and Transfection" on page 8827 of Bertin et al.) in order to identify various ligand-specific, G-protein-specific, and functional domains of these receptors (Fuller et al. column 7, line 66 – column 8, line 18). In addition, the claims of the present invention do not require that any chimeras between CaR, mGluR or $GABA_B$ receptors be made, which means that the entire full-length receptor (an extracellular, transmembrane and intracellular domain) of only *one* of either the CaR, mGluR, or $GABA_B$ receptor can be fused to a G-protein. One of ordinary skill in the art would not even need to be motivated to produce a *chimera* in this situation. All that would be required in this situation is that the artisan would merely need to substitute the entire cDNA of either the CaR, mGluR, or $GABA_B$ receptor for the entire cDNA of the β2-adrenergic receptor of Bertin et al. Regardless, one of ordinary skill in the art would have been motivated to produce a fusion protein comprising one or more domain from one or more of a CaR, mGluR, or a $GABA_B$ receptor since the functional consequences of the specific interaction between a receptor and a given G-protein subtype are difficult to analyze in intact cells, since most G-porteins are ubiquitous. Therefore, precoupling a receptor to a G-protein subunit by a physical link might focus the receptor-mediated signal toward a more potent and/or a more selective targeting of a single cellular effector (page 8827, left column, last paragraph of Bertin et al.). Again, the artisan would have had a reasonable expectation of success in producing these fusion receptors since the DNA for all of these receptors was known and the technology to produce fusion proteins was well-known and highly successful in the art at the time of the invention.

Neither Fuller et al., Kaupmann et al., or Bertin et al. teach the use of Gα15 and Gα16. However, Negulescu et al. do teach that Gα15 and Gα16 are promiscuous G-proteins. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have produced a fusion protein which is coupled to a promiscuous G-protein, such as Gα15 or Gα16, since these G-proteins allow them to couple to G-protein coupled receptors which normally couple to G-proteins of other families. These G-proteins also couple with a downstream effect, PLCβ (Negulescu et al. page 2, last paragraph). Therefore, one of ordinary skill in the art would have been motivated to produce a G-protein fusion protein comprising the promiscuous G-proteins, Gα15 or Gα16 since the production of chimeric

G-protein coupled receptors usually alters the function of these receptors as compared to wild-type and, though, these fusion (chimeric) receptors may be expressed on the cell surface of a transfected cell, it would not be clear if these receptors were functional. Due to the substitution of various domains in order to produce a chimeric receptor, the ability of the carboxyl tail of the chimera, unlike the wild-type receptor, may lose its ability to associate and activate G-proteins. Therefore, even though this protein may still retain function, it would not be known to the artisan since the affinity for the "normal" G-protein, or its ability to couple to downstream effectors, may be lost. Therefore, the use of a promiscuous G-protein would produce a high probability of success that if the G-protein chimera was functionally active, that this activity would be detected and further characterization of this chimera could continue. There would be a reasonable expectation of success in performing this invention since vectors and host cells comprising these promiscuous G-proteins have already been produced and characterized (Examples 4 – 8 of Negulescu et al).

Finally, neither Fuller et al., Kaupmann et al., Negulescu et al or Bertin et al. teach a linker of 3-30 amino acids. However, Rock et al. teach a fusion protein in which two peptides are linked via their carboxy termini a nine amino acid peptide linker (Abstract), which meets the limitation of claim 3. It would have been obvious for one of ordinary skill in the art at the time of the present invention to have used linker peptides to link the carboxy terminus of the claimed intracellular domain of the present invention to a G-protein in order to provide the G-protein with more flexibility in order to be able to adopt the proper conformation with which to optimally interact with the intracellular domain of the fusion protein. The artisan would have been motivated to use a flexible peptide linker since directly fusing two peptides which normally interact under physiologic conditions, such as a G-protein and an intracellular domain of a G-protein coupled receptor of the present invention, would constrain the movement of these peptides and may not allow for them to interact as they would if they were not fused (i.e. under physiologic conditions). One of ordinary skill in the art would have had a reasonable expectation of success in producing a fusion protein with a peptide linker since the use of peptide linkers to produce fusion proteins is well-known in the art and requires only basic recombinant DNA techniques.

9. Conclusion

A. No claim is allowable

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
July 15, 2002